

Incidence of New-onset and Flare of Preexisting Psoriasis During Rituximab Therapy for Rheumatoid Arthritis: Data from the French AIR Registry

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ABSTRACT. *Objective.* Psoriasis could be a paradoxical reaction to tumor necrosis factor- α antagonist therapy and it has been reported with rituximab therapy. Our objective was to assess the rates of new-onset and flare of preexisting psoriasis in patients taking rituximab for rheumatoid arthritis (RA).

Methods. The nationwide multicenter prospective AutoImmunity and Rituximab (AIR) registry was set up in 2006 by the French Society for Rheumatology to collect data on patients taking rituximab for joint diseases. We identified patients with RA in the registry who had psoriasis listed as an adverse drug reaction, and we obtained additional information from their physicians if needed. We computed the incidence rates of new-onset and flare of preexisting psoriasis according to the rituximab exposure time.

Results. Among the 1927 patients in the registry with RA, 2 had new-onset and 5 had flare of preexisting psoriasis after a median followup of 39.2 weeks. Incidence rates were 1.04/1000 person-years (95% CI 0.13 to 3.8) for new-onset psoriasis and 2.6/1000 person-years (95% CI 0.84 to 6.1) for flare of preexisting psoriasis. Rituximab rechallenge in the 2 new-onset cases and in 2 flare cases was not followed by recurrence or exacerbation of psoriasis. Two of the 5 flare cases developed after discontinuation of methotrexate.

Conclusion. Despite the small number of cases observed, leading to wide CI, the incidence rates in our study do not support a causative role of rituximab therapy in new-onset or flare of preexisting psoriasis in patients with RA. (First Release April 15 2012; J Rheumatol 2012;39:893–8; doi:10.3899/jrheum.111347)

Key Indexing Terms:

RHEUMATOID ARTHRITIS

RITUXIMAB

PSORIASIS

Rituximab is an anti-CD20 murine/human monoclonal antibody that causes B cell depletion. Rituximab was first licensed for use in the European Union for non-Hodgkin's lymphoma, in 1998. In June 2006, rituximab combined with methotrexate (MTX) was approved for adults with severe

active rheumatoid arthritis (RA) and an inadequate response or intolerance to other disease-modifying antirheumatic drugs (DMARD) including 1 or more tumor necrosis factor- α (TNF- α) antagonists. In clinical trials of rituximab, common adverse events were bacterial and viral infections, neutro-

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penia, thrombocytopenia, infusion-related reactions, pruritus, rash, nausea, fever, asthenia, and headache. Psoriasis is not listed among adverse events in the Summary of Product Characteristics¹.

TNF- α antagonists are effective in the treatment of psoriasis. Nevertheless, over several years of widespread use of TNF- α antagonists, several paradoxical cases of new-onset or flare of preexisting psoriasis have been reported^{2,3,4,5,6,7,8,9,10,11}. Although some of the patients had Crohn's disease or ankylosing spondylitis, others had RA, a disease that is not associated with an increased prevalence of psoriasis. The paradoxical occurrence of psoriasis during TNF- α antagonist therapy was assumed to indicate a class effect. The incidence rate of new-onset psoriasis during TNF- α antagonist therapy was recently estimated at 1.04/1000 person-years (95% CI 0.67 to 1.54)¹² in RA and 0.6% to 5.3% in other diseases¹³.

In pivotal clinical trials of rituximab, no cases of new-onset or flare of preexisting psoriasis were reported^{14,15,16,17,18,19}. However, the sample sizes were limited (18 to 316 patients) and followup was rather short (24 weeks). Between 2007 and 2009, 5 cases of new-onset psoriasis were reported in patients with RA taking rituximab^{20,21,22}.

The objective of our study was to evaluate the potential role for rituximab in new-onset and flare of preexisting psoriasis in patients with RA. We used data from the nationwide prospective multicenter AutoImmunity and Rituximab (AIR) registry maintained in France since 2006²³.

MATERIALS AND METHODS

The AIR registry. Details on the recruitment, baseline examination, and followup of patients for the AIR registry have been published²³. Briefly, it is a large multicenter prospective registry in France with the primary objective of monitoring the safety and effectiveness of rituximab in everyday clinical practice. It was set up in 2006 by the French Society for Rheumatology and the Club Rhumatismes et Inflammation. The AIR registry includes all patients with confirmed refractory autoimmune diseases treated with rituximab.

The following data are collected from each registry patient at the time of the first rituximab infusion: age, sex, disease duration, TNF- α antagonists used, and history of psoriasis and other medical events. Every 3 to 6 months, clinical nurses use standardized case-report forms to collect general health information, medications given to treat RA, treatment since the last visit, discontinued medications and reasons for discontinuation, global evaluation of the disease, and joint counts. All adverse events after initiation of rituximab are recorded using a predefined list that included the items "cutaneous eruptions" and "psoriasis." For each adverse event, the corrective treatments, outcome, and date of resolution are recorded. For psoriasis, histological results, if obtained, are described. If necessary, relevant information can be added in a specific free-text file.

Our study was conducted in patients with RA according to American College of Rheumatology (ACR) criteria included in the AIR registry between September 2006 and September 2009 who had at least 1 followup visit.

Identification of cases. We searched the AIR registry database for patients with "psoriasis" listed among adverse events. The case-report forms of these patients were reviewed by 3 investigators who were not involved in patient care (LT, AE, FM). We also searched for patients with "cutaneous eruption" listed among adverse events and reviewed their free-text files for information suggesting psoriasis-like disease.

When psoriasis was checked in the adverse events list or described in the free-text file, the following data were collected: new-onset occurrence or flare of preexisting psoriasis, site of involvement, clinical characteristics, histological findings if available, specific corrective treatment, if any, and outcome. When information on any of these points was missing from the database, we contacted either the clinical department where the patient was followed or the family doctor. We then recorded the following information in the charts: confirmation by a dermatologist or rheumatologist, history of psoriasis in the patient and family, site of involvement, psoriasis treatment and outcome, major potentially triggering psychological events, and concomitant treatments.

Our study was authorized by the relevant French authorities (French Data Protection Authority and Consultative Committee on Data Processing in Health Research). Written informed consent was obtained from all patients.

Statistical analysis. We used data recorded in the AIR registry until September 17, 2009. We determined patient-years of followup from the first rituximab infusion and any of the following: psoriasis, death, loss to followup, or end of the study period (September 17, 2009). Incidence rates of new-onset or flare of preexisting psoriasis were computed per 1000 patient-years, with 95% CI obtained using the Poisson distribution. Qualitative variables were described as number (percentage) and quantitative variables as mean (SD) or median (interquartile range) as appropriate. The data were analyzed using Stata software (Release 9.1, 2005, StataCorp, College Station, TX, USA).

RESULTS

Among the AIR registry patients, 1964 had RA; 78.7% were women and 78.1% had taken TNF- α antagonists. Table 1 reports their main characteristics. There was at least 1 followup visit for 1927 patients. For 9 of these patients, psoriasis after initiation of rituximab therapy was recorded in the database. Upon review, 2 of these 9 patients were determined to have had diffuse eczematiform eruptions. Of the 7 remaining patients, 2 experienced new-onset psoriasis and 5 flares of preexisting psoriasis. The 2 new-onset cases are described below with additional information in Table 2.

New-onset psoriasis (2 patients). Patient 1 with new-onset psoriasis: a 66-year-old woman had been diagnosed with RA 23 years earlier. She met 4 ACR criteria including symmetric arthritis and joint destruction and had negative tests for rheumatoid factor (RF) and anticitrullinated protein antibodies (ACPA). Neither she nor her family had a history of psoriasis or psoriatic arthritis. She received standard DMARD therapy including MTX and cyclosporine, which gradually lost effectiveness. Infliximab therapy was associated with recurrent urinary tract infections. Etanercept failed to prevent disease progression. In June 2008, she received 2 rituximab infusions (1000 mg 4 weeks apart), after premedication with intravenous methylprednisolone (120 mg). Concomitant medications were MTX (10 mg/week) and prednisone (7 mg/day). Upon evaluation 6 months later, the rheumatologist noted decreases in the tender and swollen joint counts and appearance of plaques of psoriasis. The location of the plaques was not specified in the case-report form. Confirmation of the diagnosis by a dermatologist was not obtained. An RA flare prompted a second rituximab course 3 weeks after the development of the psoriasis lesions. No exacerbation of these lesions was recorded in the case-report form after the first

Table 1. Baseline characteristics of patients with rheumatoid arthritis in the AutoImmunity and Rituximab registry.

Characteristic	Total, n = 1964	Patients with History of Psoriasis, n = 132
Female, n (%)	1546 (78.7)	89 (67)
Age at inclusion, yrs, mean (SD)	57.5 (20.5)	57.7 (11.4)
Disease duration at inclusion, yrs, median (IQR)	13 (8–20)	10 (7–19)
Rheumatoid factor-positive, n (%)	1333 (67.9)	76 (66.7)
ACPA, n (%)	1355 (69)	63 (66.3)
History of psoriasis, n (%)	132 (7)	—
Previous TNF- α antagonist treatments, n (%)	1594 (78.1)	107 (81.1)
1	449 (22.9)	29 (27.1)
2	686 (34.9)	47 (43.9)
3	399 (20.3)	31 (29.0)

TNF: tumor necrosis factor; IQR: interquartile range; ACPA: anticitrullinated protein antibodies.

Table 2. Characteristics of patients with new-onset psoriasis after rituximab (RTX) therapy for rheumatoid arthritis (RA).

Patient	Sex	Age at RA Diagnosis, yrs	Age at RTX Treatment, yrs	Disease Duration, yrs	No. Previous DMARD	No. Previous TNF- α Antagonists	No. RTX Courses	Disease Activity (VAS)				Efficacy of RTX on VAS Score
								Before RTX	After 1st RTX Course	After 2nd RTX Course	After 3rd RTX Course	
1	F	25	48	23	2	2	2	MD	6 mo: 62	MD	NA	No
2	F	70	77	9	2	1	3	25	4 mo: 30; 15 mo: 50	3 mo: 20; 12 mo: 50	3 mo: 30; 7 mo: 40; 9 mo: 40	Yes

VAS: visual analog scale; TNF: tumor necrosis factor; DMARD: disease-modifying antirheumatic drugs; NA: not applicable; MD: missing data.

infusion of this second course, and the lesions cleared before the second infusion. No skin biopsy was performed.

Patient 2 with new-onset psoriasis: a 79-year-old woman with a 9-year history of RA met 5 ACR criteria including symmetric arthritis and joint destruction. She had negative tests for RF and ACPA. Neither she nor any family member had a history of psoriasis or psoriatic arthritis. Despite standard DMARD therapy including MTX and hydroxychloroquine, she had progressive disease. She experienced peripheral neuropathy during etanercept treatment and was then given 3 standard rituximab courses (1000 mg twice at a 2-week interval in September 2006, January 2008, and June 2009), combined with MTX (15 mg weekly) and prednisone (6 mg per day). She reported plaques over her elbows 2 weeks after the second course. Her description of the lesions led the rheumatologist to diagnose psoriasis retrospectively. The lesions were never seen by a rheumatologist or dermatologist; no skin biopsy was performed. The lesions resolved fully after a few weeks, with no recurrences. She reported a diagnosis of a serious disease in a family member at the time of the eruption. No skin lesions developed after the third rituximab course.

Incidence of new-onset psoriasis. The incidence rate based on the 2 cases of new-onset psoriasis was 1.04/1000 patient-years (95% CI 0.13 to 3.8). After exclusion of Patient 2, in whom the diagnosis of psoriasis was doubtful, the incidence rate was 0.52/1000 patient-years (95% CI 0.01 to 2.9; Table 3).

Flare of preexisting psoriasis (5 patients). Clinical features. All 5 patients with flare of preexisting psoriasis after rituximab therapy had a history of TNF- α antagonist therapy (Table 4). Among them, 2 were diagnosed with psoriasis before initiation of TNF- α antagonist; neither patient experienced psoriasis flares during TNF- α antagonist therapy. One of them developed psoriasis lesions on her scalp 4 months after the second infusion of the third rituximab course, with confirmation of the diagnosis by a dermatologist, and improvement of the lesions within 3 months. In the other patient, palmoplantar pustular psoriasis developed on the hands and feet 4 months after the first course, which coincided with discontinuation of MTX; the lesions improved with topical treatment. In the other 3 patients, psoriasis developed during TNF- α antagonist therapy (adalimumab in 2 patients and infliximab and etanercept in 1). In 1 of these 3 patients, psoriatic lesions developed over the legs 4 months after the second infusion of the first rituximab course and resolved after topical glucocorticoid therapy; she received 2 further rituximab courses, with no further recurrences of psoriasis. In another patient, palmoplantar pustular psoriasis developed on the hands, elbows, and feet 7 months after the second infusion of the first rituximab course, then cleared spontaneously; MTX therapy was discontinued in this patient before initiation of rituximab. The remaining patient experienced an exacerbation of psoriasis lesions on her legs 8 months after the second

Table 3. Rates of new-onset and flare of preexisting psoriasis in patients who were given rituximab for rheumatoid arthritis and who had at least 1 followup visit.

	Rituximab, n = 1927
Patient-years of rituximab exposure	1921.9
New-onset psoriasis, no. patients	1* or 2†
Rate of new-onset psoriasis/1000 patient-years (95% CI††)	
Counting 1 case*	0.52 (0.01 to 2.9)
Counting both cases†	1.04 (0.13 to 3.8)
Rate of flare of preexisting psoriasis/1000 patient-years (95% CI††)	2.6 (0.84 to 6.1)

* Psoriasis diagnosed by a rheumatologist. † Lesions reported by the patient but not seen by a physician. †† Poisson distribution.

infusion of the second rituximab course; the lesions improved after topical glucocorticoid therapy and no exacerbation was noted after the third rituximab course given 9 months after the last infusion of the second course.

These 5 patients represented 4% of the 132 AIR registry patients who had a history of psoriasis.

Incidence of flare of preexisting psoriasis. The incidence rate of flare of preexisting psoriasis was 2.6/1000 patient-years (95% CI 0.84 to 6.11; Table 3).

History of psoriasis (132 patients). Among the 132 patients who had a history of psoriasis, 11 experienced psoriasis exacerbations during TNF- α antagonist therapy (adalimumab, n = 7; infliximab, n = 2; adalimumab and etanercept, n = 1; and infliximab and etanercept, n = 1), including 3 patients with exacerbations after rituximab therapy. Thus, 8 patients with a history of psoriasis during TNF- α antagonist therapy did not have any exacerbations after receiving rituximab. The characteristics of these patients are summarized in Table 1.

DISCUSSION

Among the 1927 patients with RA treated with rituximab who

had at least 1 followup visit, 1 had physician-diagnosed new-onset psoriasis and 1 had self-reported new-onset psoriasis. The incidence rate of new-onset psoriasis was 0.52/1000 patient-years (95% CI 0.01 to 2.9) when only the confirmed case was counted and 1.04/1000 patient-years (95% CI 0.13 to 3.8) when both cases were counted. In addition, 5 patients had confirmed flare of preexisting psoriasis, yielding an incidence rate of 2.6/1000 patient-years (95% CI 0.84 to 6.1).

Our study has several limitations. Underreporting may have occurred²³, and the diagnosis of psoriasis was not routinely confirmed by a dermatologist. No biopsies were performed. The small number of events yielded wide CI for the incidence rates. The strong points of our study are the large number of patients exposed to rituximab, and case ascertainment by physicians who were not involved in patient care. To our knowledge, these results from a large observational cohort are the first available data on the incidence of new-onset and flare of preexisting psoriasis during therapy with rituximab.

In the main randomized phase III studies^{17,18,19} evaluating the efficacy and the safety of rituximab in RA in 511, 378, and 559 patients, respectively, no cases of psoriasis were recorded among the drug-related adverse events. However, as early as 2007, 3 reports of psoriasis in previously unaffected patients who had no history or risk factors for the disease were published. One of these patients experienced scalp psoriasis 6 months after rituximab therapy; another had psoriatic plaques over both knees and on the thighs 4 months after rituximab therapy; and the remaining patient had extensive psoriasis over the elbows, arms, thighs, and torso 4 months after rituximab therapy. The underlying diagnoses were RF-positive RA, RF-negative RA, and systemic lupus erythematosus²⁰. More recently, a case of psoriasis with psoriatic arthritis 6 to 8 weeks after the first rituximab infusion in a 66-year-old woman with non-Hodgkin's lymphoma was reported²¹, as well as psoriatic skin lesions occurring 10 days after the first infusion of the second rituximab course in a patient with RA²². One case of pso-

Table 4. Characteristics of patients with flare of preexisting psoriasis after rituximab (RTX) therapy for rheumatoid arthritis (RA).

Patient	Sex	Age at RA Diagnosis, yrs	Age at RTX Treatment, yrs	Disease Duration, yrs	No. Previous DMARD	No. Previous TNF- α Antagonists	No. RTX Courses	Disease Activity (VAS)				Efficacy of RTX on VAS Score
								Before RTX	After 1st RTX Course	After 2nd RTX Course	After 3rd RTX Course	
1	F	37	41	6	2	3	3	65	4 mo: 20; 6 mo: 13	1.5 mo: 2; 6 mo: 10	1.5 mo: 15; 6 mo: 12	Yes
2	F	66	73	7	3	3	2	70	2 mo: 50; 5 mo: 40; 7 mo: 80	MD	NA	No
3	F	48	58	12	5	3	3	90	6 mo: 40	6 mo: 29; 10 mo: 40	3 mo: 45	No
4	F	45	60	17	4	2	1	70	3 mo: 30; 6 mo: 20; 12 mo: 60	NA	NA	No
5	F	60	67	9	3	2	3	MD	3 mo: 30; 9 mo: 60	2 mo: 100; 9 mo: 50	MD	No

VAS: visual analog scale; DMARD: disease-modifying antirheumatic drugs; TNF: tumor necrosis factor; NA: not applicable; MD: missing data.

riasis required hospitalization²⁰, and those 3 cases were more severe than the 2 cases we have reported.

Further, these 5 cases of psoriasis during rituximab therapy were not linked by a consistent clinical pattern, time-course, or site of involvement. Nevertheless, a potential role for rituximab was suggested. Hypotheses regarding possible mechanisms include an effect of B cell depletion on the function of T cells, whose translocation from the dermis into the epidermis is a key event in psoriasis. Further, rituximab therapy is associated with an increased rate of infections, and infections have been described as triggers for psoriasis^{20,21,22}.

The AIR registry does not have an internal control population composed of RA patients who were not exposed to rituximab. Therefore, we cannot directly determine whether rituximab therapy affects the incidence of psoriasis. Nevertheless, the incidence of psoriasis in the general population was recently estimated at 0.8 per 1000 in Rochester, MN, USA; and 1.4 per 1000 in the UK^{24,25}. These rates are similar to the rate of new-onset psoriasis in our cohort. In the British Society for Rheumatology Biologics Register (BSRBR), the incidence of psoriasis in patients with RA was similar to that in the general population¹². Thus, of 2880 RA patients with 5207 patient-years of exposure to standard DMARD, none experienced new-onset psoriasis, producing an incidence rate of 0 with an upper 97.5% CI boundary of 0.71. The 95% CI in our study contain this value, suggesting that rituximab therapy probably did not increase the risk of new-onset psoriasis in patients with RA. Although the wide 95% CI of our study and the low incidence rate of the DMARD control group of the BSRBR preclude a definitive conclusion. Further, rituximab rechallenge in the 2 patients with new-onset psoriasis was not associated with recurrences or exacerbations of the lesions, suggesting that causality was “doubtful” at most.

No data are available on the recurrence rates of psoriasis in populations of patients with psoriasis or joint disease. Therefore, we cannot determine whether the risk of flare of preexisting psoriasis was affected by rituximab therapy in our cohort. It should be noted that causality was doubtful in 4 of our 5 cases of flare of preexisting psoriasis: in 2 of these cases, recent MTX withdrawal probably played a role and in the other 2 cases no further recurrences were noted during continued rituximab therapy.

More than 75% of the patients in the AIR registry have had prior exposure to anti-TNF, which could have influenced the propensity of these patients to develop drug-induced psoriasis. However, this reflects “real life” RA treatment since rituximab is only a second-line biologic drug in RA and most patients with RA receive anti-TNF drugs before rituximab.

Although no firm conclusion can be drawn, these data do not support an increased risk of flare of preexisting psoriasis in patients who are given rituximab.

Our data do not support a causative role of rituximab in the induction or exacerbation of psoriasis in patients with RA. They require confirmation in further studies.

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